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BAKER, A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary

Application No.	Applicant(s)
09/353,423	Tattanahalli et al.
Examiner	**Group Art Unit**
Anne-Marie Baker, Ph.D.	1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-39 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-39 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-39 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-12 are directed to a method for providing a patient with an interferon α (IFNα) polypeptide. Claims 13-18 are directed to a method for increasing interferon α levels in a patient. Claims 19-29 are directed to a recombinant vector comprising a nucleic acid segment encoding an interferon α polypeptide, wherein the interferon α polypeptide lacks a secretion leader sequence. Claims 30-33 are directed to a pharmaceutical formulation comprising a recombinant vector comprising a nucleic acid segment encoding an interferon α polypeptide, wherein the interferon α polypeptide lacks a secretion leader sequence. Claims 34-39 are directed to a method of treating hepatocellular carcinoma in a mammal.

The specification fails to provide an enabling disclosure for the claimed methods and compositions because the specification teaches that the only use for the methods and compositions is for gene therapy, but the specification does not enable this use. The specification does not teach how to use the claimed methods and compositions in gene therapy applications, for the following reasons.

The claims are directed to methods of gene therapy. However, gene therapy is not routinely successful. Therefore, the disclosure must enable the full scope of the claimed methods with specific guidance. However, the specification fails to teach any method for transferring an IFNα gene into a target cell and expressing that gene at a level sufficient to produce a therapeutic effect in a diseased immunocompetent animal. The specification does not provide any guidance as to the level of gene expression required, the number of transduced cells needed, the route and time course of administration, the site of administration, when, where, or for how long the IFNα gene should be expressed, the frequency of administration of the IFNα-encoding gene therapy vector required, or in some embodiments, the intended target tissue, for treatment of any pathological condition in an immunocompetent animal. The specification also lacks any working examples showing that the contemplated IFNα-encoding vector, once delivered to the appropriate site, would be expressed at a level sufficient to provide adequate product to effect the desired therapy in an immunocompetent animal. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can

point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed methods and compositions for *in vivo* gene therapy. Thus, absent any showing that the claimed methods and compositions can be used in gene therapy applications to produce the intended therapeutic effect in an immunocompetent animal, such as a human, the claims directed to gene therapy are not enabled by the disclosure.

The specification fails to provide an enabling disclosure for use of the claimed methods for the treatment of any disease because the specification does not offer specific guidance for treating any disease in an immunocompetent animal. The claims encompass use of the method for the treatment of any disease, including for example hairy cell leukemia, Kaposi's sarcoma, renal cell carcinoma, non-Hodgkin's lymphoma, T-cell leukemia, multiple and chronic myelogenous leukemia, malignant melanoma, bladder cell carcinoma, colon carcinoma, condyloma acuminata, rhinovirus and various forms of chronic viral hepatitis occurring as a result of hepatitis B virus (HBV), hepatitis C virus (HCV), non-A non-B virus (NANB), or hepatitis δ virus (HDV) infection, megakaryocytopoiesis, and thrombocytosis (see Specification p. 1, line 17 to p. 2, line 5), but the specification does not offer specific guidance for the treatment of any of these diseases. As gene therapy is not routine for the reasons discussed above, undue experimentation would have been required for one skilled in the art to treat any disease using the claimed method.

The specification fails to provide an enabling disclosure for targeting appropriate cells for the treatment of any of the aforementioned diseases. The *in vivo* working example in the specification is limited to testing adenoviral vectors in a nude mouse model of hepatocellular carcinoma. Specific guidance in the disclosure is limited to targeting hepatic tissue. The specification indicates that targeting can be achieved by use of the α-fetoprotein (AFP) promoter in combination with administration through the intrahepatic artery. No such specific guidance is offered with regard to the treatment of any other type of disease. The

specification does not teach how to target a vector using any other mode of administration. Only general guidance is offered with regard to targeting strategies known in the art. However, the art recognizes that targeting strategies are not currently sufficient to overcome the problems known in the art. The instant specification admits that "the inability to target the tissue of interest is one of the major challenges of gene therapy" (p. 2, lines 8-9). However, the disclosure does not offer a solution to this problem beyond the targeting of hepatic tissue. While progress has been made in recent years for *in vivo* gene transfer, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings in the art. For example, Miller et al. (1995) review the types of vectors available for *in vivo* gene therapy, and conclude that "for long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain et al. (1998) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain et al. review new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) review vectors known in the art for use in gene therapy and discuss problems associated with each type of vector. The teachings of Verma et al. indicate that a resolution to vector targeting has not been achieved in the art (see entire article). Verma et al. also teach that appropriate regulatory elements may improve expression, but that it is unpredictable which tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal et al. (1995) also review various vectors known in the art and indicate

that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Even expression studies in animals are often not predictive that the same or similar results can be achieved in patients or that such expression would alleviate clinical symptoms. For example, although researchers have demonstrated expression of the CFTR gene in the surface airway cells of laboratory animals, problems transferring sufficient quantities of the CFTR gene into patients' cells have prevented the method from providing therapeutic benefit. Furthermore, the viral vector used to transfer the gene provoked an immune reaction in some patients (Marshall, 1995, p. 1052). Marshall emphasizes that the central challenge in the field of gene therapy is to find safe vectors capable of transporting genes efficiently into target cells, and getting the cells to express the genes once they are inserted. These problems remain unresolved. Thus, the claims directed to *in vivo* gene therapy are not enabled because the specification fails to disclose a method for transferring an IFNα gene into the appropriate cells and expressing that gene at a therapeutic level.

The instant specification describes one working example demonstrating *in vivo* administration of an IFNα-encoding adenoviral vector (p. 20, line 21 to p. 21, line 11). However, the *in vivo* working example is limited to testing the adenoviral vectors in a nude mouse model of hepatocellular carcinoma. The results are presented in Figure 10. The working example demonstrates that adenoviral vectors encoding both the secreted form and non-secreted form of IFNα2b resulted in a reduction of tumor size. The mice were treated with daily injections of $1x10^{10}$ particles of recombinant adenoviral vectors for seven days.

For the reasons discussed herein above, animal studies have not been predictive in the gene therapy art. Studies that rely on nude mouse models for the testing of cancer treatments are particularly non-predictive. Anticancer treatments effective in nude mouse tumor models are not predictive of similar success in human patients. Gura (1997) reports that xenograft models, in which human tumors are implanted

underneath the skin of mice with faulty immune systems, are not predictive in the screening of candidate anticancer compounds, mainly because xenograft tumors do not behave like naturally occurring tumors in humans. For example, they do not spread to other tissues. Alan Oliff states that "[t]he fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (p. 1041, paragraph 2). The article further makes the point that cell culture systems provide no information about whether a drug will make it to the tumor site and that the results cannot tell a researcher how anticancer drugs will act in the body (p. 1042, column 2, paragraph 1).

Furthermore, it is well-known in the art that re-administration of adenoviral vectors is not effective in immunocompetent animals because an immune response is provoked which prevents expression upon re-administration. The *in vivo* working example involves daily injections of recombinant adenoviral vector for seven days. As nude mice are immunodeficient, clearance of the adenoviral vector is not an issue in this system and expression sufficient to produce an anti-tumor effect is observed. However, the immune response in immunocompetent animals severely limits expression of the vector upon re-administration. Verma et al. (1997) discuss the immune reaction to adenoviral vectors at page, 241, column 1, paragraph 3 to column 2, paragraph 2. The authors state that "the immune system is behind the short-term expression that is usually obtained from adenoviral vectors" (page 241, column 1, paragraph 3) and that "[t]he immune reaction is potent, eliciting both the cell-killing 'cellular' response and the antibody-producing 'humoral' response" (page 241, column 1, paragraph 4). Furthermore, Verma et al. state that "[u]nfortunately for gene therapy, most of the human population will probably have antibodies to adenovirus from previous infection with the naturally occuring virus" (page 241, column 1, paragraph 4). Kass-Eisler et al. (1994) report that "adults could not be boosted by a second administration of virus, presumably due to the presence of high levels of neutralizing antibodies" (abstract). Yang et al. (1996) report that the destruction of adenovirus-infected

hepatocytes is due to CTL responses to both viral antigens and the transgene product. Thus, the immune response to adenoviral vectors can be expected to have a pronounced effect on IFNα gene expression in an immunocompetent animal and experiments performed in immunodeficient animals would therefore not be expected to be predictive of results obtainable in immunocompetent animals. While the instant specification contemplates that immunosuppression can be used in combination with the administration of viral vectors (p. 22, lines 21-25), specific guidance is not provided for adequately suppressing the immune response to the extent required to obtain transgene expression sufficient to produce a therapeutic effect.

The specification fails to provide an enabling disclosure for the use of any vector encoding an IFNα gene because the specification does not offer specific guidance for the use of any vector other than a recombinant adenoviral vector. The *in vivo* working example is limited to testing adenoviral vectors in a nude mouse model. While other vector systems known in the art are contemplated for use in the instant invention (pp. 7, 17, and 24), only general teachings are provided with regard to their use. No specific guidance is offered for the use of vectors, other than adenoviral vectors, to generate expression sufficient to produce a therapeutic effect.

With regard to the claimed vectors, the specification teaches that the utility for the vectors is for therapy, in general and for the treatment of tumors, in particular, but the specification does not teach how to use the vectors in gene therapy applications for the reasons discussed herein above. With regard to the pharmaceutical compositions, the term "pharmaceutical" denotes an intended use (i.e., for therapy), but the disclosure is not enabling for the intended use.

With regard to Claim 36, which recites that "the mammalian subject is a human being," the specification fails to provide an enabling disclosure for the claimed method of treating hepatocellular

carcinoma in a human being because a human being is an immunocompetent animal and the specification is not enabling for treatment of an immunocompetent animal, for the reasons discussed herein above.

In view of the quantity of experimentation necessary to determine appropriate parameters for the claimed method for treatment of a pathological condition in immunocompetent animals, and given the lack of applicable working examples demonstrating an *in vivo* effect in an immunocompetent animal, the limited guidance in the specification, the broad scope of the claims, the state of the art at the time the invention was made, the limited working example for *in vivo* gene therapy in a nude mouse model carrying a xenografted tumor, and the unpredictability for using the claimed methods and compositions in any gene therapy application to produce the desired therapeutic effect, undue experimentation would have been required for one skilled in the art to practice the claimed invention and to make and use the claimed compositions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-18 and 34-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-18 are indefinite because the claimed method does not recite an increase in interferon levels as stated in the preamble, but rather only recites that the interferon is expressed in the tissue of interest. Thus, the claims are confusing.

Claim 18 is indefinite in its recitation of "wherein the tissue comprises cells *in vivo*" because it is unclear when the tissue would not be *in vivo*, as Claim 13 recites that it is in a patient, which is equivalent to being *in vivo*. Thus, it is unclear how Claim 18 is further limiting.

Claims 34-39 are indefinite because the method does not recite that the administration of the vector results in any effect, such as treatment, as recited in the preamble. The preamble recites "a method of treating hepatocellular carcinoma," but the method does not provide for any such effect, but rather only involves the administration of a vector.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Given that the term "patient" is not defined in the specification, the term is interpreted as broadly as reasonable. Therefore, the following art rejection is set forth with the understanding that the term "patient" reads broadly on any mammal, e.g. any mammal involved in an experimental or clinical trial, whether healthy or unhealthy. The enablement rejection set forth above is only directed to enablement for the asserted utility of gene therapy. Thus, while the specification is not enabling for the only asserted utility, the claims read broadly on methods of *in vivo* gene delivery and do not recite a therapeutic effect.

Claims 1-4, 10, 11, 13, 14, 17, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,069,133 (Chiou et al., 2000).

Chiou et al. (2000) disclose and claim a method of *in vivo* IFNα gene delivery to liver cells. See Claim 1 of Chiou et al.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker
Patent Examiner